August 2015

Prograf Ampoules 5mg/ml Concentrate for solution for infusion
(Tacrolimus 5mg/ml)

Prograf Capsules
(Tacrolimus 0.5 mg, 1 mg, and 5 mg per capsule)

Physicians’ Prescribing Information (for Ampoules and Capsules)

Additions appear as underlined text, deleted text as strikethrough

Special warnings and special precautions for use

The combined administration of ciclosporin and tacrolimus should be avoided and care should be taken when administering tacrolimus to patients who have previously received ciclosporin (see sections 4.2 and 4.5).

High potassium intake or potassium-sparing diuretics should be avoided (see section 4.5).

Certain combinations of tacrolimus with drugs known to have nephrotoxic or neurotoxic effects may increase the risk of these effects (see section 4.5).

Vaccination
Immunosuppressants may affect the response to vaccination and vaccination during treatment with tacrolimus may be less effective. The use of live attenuated vaccines should be avoided.

Gastrointestinal disorders
Gastrointestinal perforation has been reported in patients treated with tacrolimus. As gastrointestinal perforation is a medically important event that may lead to a life-threatening or serious condition, adequate treatments should be considered immediately after suspected symptoms or signs occur.

Since levels of tacrolimus in blood may significantly change during diarrhoea episodes, extra monitoring of tacrolimus concentrations is recommended during episodes of diarrhoea.
The combined administration of ciclosporin and tacrolimus should be avoided and care should be taken when administering tacrolimus to patients who have previously received ciclosporin (see sections 4.2 and 4.5).

Cardiac disorders
Ventricular hypertrophy or hypertrophy of the septum, reported as cardiomyopathies, have been observed on rare occasions. Most cases have been reversible, occurring primarily in children with tacrolimus blood trough concentrations much higher than the recommended maximum levels. Other factors observed to increase the risk of these clinical conditions included pre-existing heart disease, corticosteroid usage, hypertension, renal or hepatic dysfunction, infections, fluid overload, and oedema. Accordingly, high-risk patients, particularly young children and those receiving substantial immunosuppression should be monitored, using such procedures as echocardiography or ECG pre- and post-transplant (e.g. initially at three months and then at 9-12 months). If abnormalities develop, dose reduction of Prograf therapy, or change of treatment to another immunosuppressive agent should be considered. Tacrolimus may prolong the QT interval and may but at this time lacks substantial evidence for causing Torsades de Pointes. Caution should be exercised in patients with risk factors for QT prolongation, including patients with a personal or family history of QT prolongation, congestive heart failure, bradyarrhythmias and electrolyte abnormalities. Caution should also be exercised in patients diagnosed or suspected to have Congenital Long QT Syndrome or acquired QT prolongation or patients on concomitant medications known to prolong the QT interval, induce electrolyte abnormalities or known to increase tacrolimus exposure (see section 4.5).

Lymphoproliferative disorders and malignancies
Patients treated with Prograf have been reported to develop Epstein-Barr-virus (EBV)-associated lymphoproliferative disorders (see section 4.8). Patients switched to Prograf therapy should not receive anti-lymphocyte treatment concomitantly. Very young (<2 years), EBV-VCA-negative children have been reported to have an increased risk of developing lymphoproliferative disorders. Therefore, in this patient group, EBV-VCA serology should be ascertained before starting treatment with Prograf. During treatment, careful monitoring with EBV-PCR is recommended. Positive EBV-PCR may persist for months and is per se not indicative of lymphoproliferative disease or lymphoma. As with other immunosuppressive agents, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

As with other potent immunosuppressive compounds, the risk of secondary cancer is unknown (see section 4.8).

Pure Red Cell Aplasia
Cases of pure red cell aplasia (PRCA) have been reported in patients treated with tacrolimus. All patients reported risk factors for PRCA such as parvovirus B19 infection, underlying disease or concomitant medications associated with PRCA.

As with other immunosuppressive agents, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

If administered accidentally either arterially or perivasally, the reconstituted Prograf 5 mg/ml concentrate for solution for infusion may cause irritation at the injection site.
Excipients
Prograf 5 mg/ml concentrate for solution for infusion contains polyoxyethylene hydrogenated castor oil, which has been reported to cause anaphylactoid reactions. Caution is therefore necessary in patients who have previously received preparations containing polyoxyethylene castor oil derivatives either by intravenous injection or infusion, and in patients with an allergenic predisposition. The risk of anaphylaxis may be reduced by slow infusion of reconstituted Prograf 5 mg/ml concentrate for solution for infusion or by the prior administration of an antihistamine. Patients should be closely observed during the first 30 minutes of infusion for possible anaphylactoid reaction.

Interaction with other medicinal products and other forms of interaction

Metabolic interactions
Systemically available tacrolimus is metabolised by hepatic CYP3A4. There is also evidence of gastrointestinal metabolism by CYP3A4 in the intestinal wall. Concomitant use of medicinal products or herbal remedies known to inhibit or induce CYP3A4 may affect the metabolism of tacrolimus and thereby increase or decrease tacrolimus blood levels. It is therefore strongly recommended to closely monitor tacrolimus blood levels as well as, QT prolongation (with ECG), renal function and other side effects, whenever substances which have the potential to alter CYP3A4 metabolism are used concomitantly and to interrupt or adjust the tacrolimus dose as appropriate in order to maintain similar tacrolimus exposure (see sections 4.2 and 4.4).

Other interactions potentially leading to increased tacrolimus blood levels
Tacrolimus is extensively bound to plasma proteins. Possible interactions with other medicinal products known to have high affinity for plasma proteins should be considered (e.g., NSAIDs, oral anticoagulants, or oral antidiabetics). Other potential interactions that may increase systemic exposure of tacrolimus include the prokinetic agent metoclopramide, cimetidine and magnesium-aluminium-hydroxide.

Protein binding considerations
Tacrolimus is extensively bound to plasma proteins. Possible interactions with other medicinal products known to have high affinity for plasma proteins should be considered (e.g., NSAIDs, oral anticoagulants, or oral antidiabetics).

Undesirable effects

Infections and infestations
As is well known for other potent immunosuppressive agents, patients receiving tacrolimus are frequently at increased risk for infections (viral, bacterial, fungal, protozoal). The course of pre-existing infections may be aggravated. Both generalised and localised infections can occur. Cases of BK virus associated nephropathy, as well as cases of JC virus associated progressive multifocal leukoencephalopathy (PML), have been reported in patients treated with immunosuppressants, including Prograf.

Neoplasms benign, malignant and unspecified (incl. cysts and polyps)
Patients receiving immunosuppressive therapy are at increased risk of developing malignancies. Benign as well as malignant neoplasms including EBV-associated lymphoproliferative disorders and skin malignancies have been reported in association with tacrolimus treatment.

Blood and lymphatic system disorders
common: anaemia, leukopenia, thrombocytopenia, leukocytosis, red blood cell analyses abnormal
uncommon: coagulopathies, coagulation and bleeding analyses abnormal, pancytopenia, neutropenia
rare: thrombotic thrombocytopenic purpura, hypoprothrombinaemia
not known: pure red cell aplasia, agranulocytosis, haemolytic anaemia

Immune system disorders
Allergic and anaphylactoid reactions have been observed in patients receiving tacrolimus (see section 4.4 under Excipients).

Endocrine disorders
rare: hirsutism

Metabolism and nutrition disorders
very common: hyperglycaemic conditions, diabetes mellitus, hyperkalaemia
common: hypomagnesaemia, hypophosphataemia, hypokalaemia, hypocalcaemia, hyponatraemia, fluid overload, hyperuricaemia, appetite decreased, anorexia, metabolic acidoses, hyperlipidaemia, hypercholesterolaemia, hypertriglyceridaemia, other electrolyte abnormalities
uncommon: dehydration, hypoproteinaemia, hyperphosphataemia, hypoglycaemia

Psychiatric disorders
very common: insomnia
common: anxiety symptoms, confusion and disorientation, depression, depressed mood, mood disorders and disturbances, nightmare, hallucination, mental disorders
uncommon: psychotic disorder

Nervous system disorders
very common: tremor, headache
common: seizures, disturbances in consciousness, paraesthesias and dysesthesias, peripheral neuropathies, dizziness, writing impaired, nervous system disorders
uncommon: coma, central nervous system haemorrhages and cerebrovascular accidents, paralysis and paresis, encephalopathy, speech and language abnormalities, amnesia
rare: hypertonia
very rare: myasthenia

Eye disorders
common: vision blurred, photophobia, eye disorders
uncommon: cataract
rare: blindness

Ear and labyrinth disorders
common: tinnitus
uncommon: hypoacusis
rare: deafness neurosensory
very rare: hearing impaired

Cardiac disorders
common: ischaemic coronary artery disorders, tachycardia
uncommon: ventricular arrhythmias and cardiac arrest, heart failures, cardiomyopathies, ventricular hypertrophy, supraventricular arrhythmias, palpitations, ECG investigations abnormal, heart rate and pulse investigations abnormal
rare: pericardial effusion
very rare: echocardiogram abnormal, electrocardiogram QT prolonged, Torsades de Pointes.
Blood and lymphatic system disorders
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uncommon: coagulopathies, coagulation and bleeding analyses abnormal, pancytopenia, neutropenia
rare: thrombotic thrombocytopenic purpura, hypoprothrombinaemia
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Ear and labyrinth disorders
common: tinnitus
uncommon: hypoacusis
rare: deafness neurosensory
very rare: hearing impaired

Vascular disorders
very common: hypertension
common: haemorrhage, thrombembolic and ischaemic events, peripheral vascular disorders, vascular hypotensive disorders
uncommon: infarction, venous thrombosis deep limb, shock

Respiratory, thoracic and mediastinal disorders
common: dyspnoea, parenchymal lung disorders, pleural effusion, pharyngitis, cough, nasal congestion and inflammations
uncommon: respiratory failures, respiratory tract disorders, asthma
rare: acute respiratory distress syndrome

Gastrointestinal disorders
very common: diarrhoea, nausea
common: gastrointestinal inflammatory conditions, gastrointestinal ulceration and perforation, gastrointestinal haemorrhages, stomatitis and ulceration, ascites, vomiting, gastrointestinal and abdominal pains, dyspeptic signs and symptoms, constipation, flatulence, bloating and distension, loose stools, gastrointestinal signs and symptoms
uncommon: ileus paralytic, peritonitis, acute and chronic pancreatitis, blood amylase increased, gastrooesophageal reflux disease, impaired gastric emptying
rare: subileus, pancreatic pseudocyst
Renal and urinary disorders
very common: renal impairment
common: renal failure, renal failure acute, oliguria, renal tubular necrosis, nephropathy
    toxic, urinary abnormalities, bladder and urethral symptoms
uncommon: anuria, haemolytic uraemic syndrome
very rare: nephropathy, cystitis haemorrhage

Skin and subcutaneous tissue disorders
common: pruritus, rash, alopecia, acne, sweating increased
uncommon: dermatitis, photosensitivity
rare: toxic epidermal necrolysis (Lyell’s syndrome)
very rare: Stevens Johnson syndrome

Musculoskeletal and connective tissue disorders
common: arthralgia, muscle cramps, pain in limb, back pain
uncommon: joint disorders

Endocrine disorders
rare: hirsutism

Metabolism and nutrition disorders
very common: hyperglycaemic conditions, diabetes mellitus, hyperkalaemia
common: hypomagnesaemia, hypophosphataemia, hypokalaemia, hypocalcaemia,
    hyponatraemia, fluid overload, hyperuricaemia, appetite decreased, anorexia,
    metabolic acidoses, hyperlipidaemia, hypercholesterolaemia,
    hypertriglyceridaemia, other electrolyte abnormalities
uncommon: dehydration, hypoproteinaemia, hyperphosphataemia, hypoglycaemia

Infections and infestations
As is well known for other potent immunosuppressive agents, patients receiving tacrolimus are
frequently at increased risk for infections (viral, bacterial, fungal, protozoal). The course of pre-
exisiting infections may be aggravated. Both generalised and localised infections can occur.
Cases of BK virus associated nephropathy, as well as cases of JC virus associated progressive
multifocal leukoencephalopathy (PML), have been reported in patients treated with
immunosuppressants, including Prograf.

Injury, poisoning and procedural complications
common: primary graft dysfunction

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Vascular disorders
very common: hypertension
common: haemorrhage, thromboembolic and ischaemic events, peripheral vascular
disorders, vascular hypotensive disorders
uncommon: infarction, venous thrombosis deep limb, shock
General disorders and administration site conditions

common: asthenic conditions, febrile disorders, oedema, pain and discomfort, blood alkaline phosphatase increased, weight increased, body temperature perception disturbed

uncommon: multi-organ failure, influenza like illness, temperature intolerance, chest pressure sensation, feeling jittery, feeling abnormal, blood lactate dehydrogenase increased, weight decreased

rare: thirst, fall, chest tightness, mobility decreased, ulcer

very rare: fat tissue increased

Immune system disorders

Allergic and anaphylactoid reactions have been observed in patients receiving tacrolimus (see section 4.4).

Gastrointestinal disorders

very common: diarrhoea, nausea

common: gastrointestinal inflammatory conditions, gastrointestinal ulceration and perforation, gastrointestinal haemorrhages, stomatitis and ulceration, ascites, vomiting, gastrointestinal and abdominal pains, dyspeptic signs and symptoms, constipation, flatulence, bloating and distension, loose stools, gastrointestinal signs and symptoms

uncommon: ileus paralytic, peritonitis, acute and chronic pancreatitis, blood amylase increased, gastrooesophageal reflux disease, impaired gastric emptying

rare: subileus, pancreatic pseudocyst

Hepatobiliary disorders

common: hepatic enzymes and function abnormalities, cholestasis and jaundice, hepatocellular damage and hepatitis, cholangitis

rare: hepatitic artery thrombosis, venoocclusive liver disease

very rare: hepatic failure, bile duct stenosis

Reproductive system and breast disorders

uncommon: dysmenorrhoea and uterine bleeding

Psychiatric disorders

very common: insomnia

common: anxiety symptoms, confusion and disorientation, depression, depressed mood, mood disorders and disturbances, nightmare, hallucination, mental disorders

uncommon: psychotic disorder

Skin and subcutaneous tissue disorders

common: pruritus, rash, alopecia, acne, sweating increased

uncommon: dermatitis, photosensitivity

rare: toxic epidermal necrolysis (Lyell’s syndrome)

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Musculoskeletal and connective tissue disorders

common: arthralgia, muscle cramps, pain in limb, back pain

uncommon: joint disorders

Renal and urinary disorders

very common: renal impairment

common: renal failure, renal failure acute, oliguria, renal tubular necrosis, nephropathy toxic, urinary abnormalities, bladder and urethral symptoms

uncommon: anuria, haemolytic uraemic syndrome
very rare: nephropathy, cystitis haemorrhagic

Reproductive system and breast disorders
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General disorders and administration site conditions
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Injury, poisoning and procedural complications
common: primary graft dysfunction

Preclinical safety data

The kidneys and the pancreas were the primary organs affected in toxicity studies performed in rats and baboons. In rats, tacrolimus caused toxic effects to the nervous system and the eyes. Reversible cardiotoxic effects were observed in rabbits following intravenous administration of tacrolimus. When tacrolimus is administered intravenously as rapid infusion/bolus injection at a dose of 0.1 to 1.0 mg/kg, QTc prolongation has been observed in some animal species. Peak blood concentrations achieved with these doses were above 150 ng/mL which is more than 6-fold higher than mean peak concentrations observed with Prograf in clinical transplantation.
CAEB2/AML10 (CAEB2), which is a type of autoantibody, is associated with a number of clinical features, including:

- Skin rash
- Gastrointestinal symptoms
- Hemorrhage
- Hemolytic anemia
- Neurological symptoms
- Renal failure
- Cardiac failure
- Pulmonary hypertension
- Septic shock
- Hematopoietic failure
- Thrombotic microangiopathy
- Torsades de Pointes
- Stevens-Johnson syndrome
- Toxic epidermal necrolysis
- Hemolytic uremic syndrome
- PRES

These clinical features are often present in patients with CAEB2, indicating the need for prompt diagnosis and treatment.
• Univew
• Chirous
• Eczeematous nodules, skin peeling
• Tender to touch
• Violent pain and swelling in the abdomen.
• Pain and tenderness in the neck, chest, abdomen, and limbs.
•blue discoloration, redness in the body and around the eyes, in the mouth, on the skin of the lips, with a severe infection, in the blood.

As shown in the table—pure cell aplasia (PC A), agranulocytosis (AGN), hemolytic anemia (HA).

Ingredients:

• 0.5 mg:
  - Titanium dioxide (E 171), yellow iron oxide (E 172), gelatin.
  - Shellac, lecithin (soya), hydroxypropyl cellulose, simethicone, red iron oxide (E 172).

• 1 mg:
  - Titanium dioxide (E 171), gelatin.
  - Shellac, lecithin (soya), hydroxypropyl cellulose, simethicone, red iron oxide (E 172).

• 5 mg:
  - Titanium dioxide (E 171), red iron oxide (E 172), gelatin.
  - Shellac, titanium dioxide (E 171) and propylene glycol.

Reduced volume of white blood cells, reduced red blood cell count, anemia.

The information is available on the recorder's website for manufacturers of the drug company.